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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/668,448	09/22/2003	Thomas R. Porter	50450-8302.US03	2356

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EXAMINER	
ZARA, JANE J	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 06/16/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/668,448	PORTER ET AL.	
	Examiner	Art Unit	
	Jane Zara	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 April 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *37-46* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *37-46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *2-3-06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This Office action is in response to the communication filed 4-21-04.

Claims 37-46 are pending in the instant application.

Claim Objections

The numbering of claims is not in accordance with 37 CFR 1.126 which requires the original numbering of the claims to be preserved throughout the prosecution. When claims are canceled, the remaining claims must not be renumbered. When new claims are presented, they must be numbered consecutively beginning with the number next following the highest numbered claims previously presented (whether entered or not).

Misnumbered claims 1-10 have been renumbered 37-46.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 37-46 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to compositions and methods for the delivery of a medicament or biological agent comprising the delivery of a plurality of filmogenic protein encapsulated insoluble gas filled microbubbles, wherein the biological agent or medicament is encapsulated in the microbubble. The specification and claims do not adequately describe the broad genus comprising filmogenic protein encapsulated microbubbles. The disclosure teaches microbubble compositions for delivery comprising approximately between 3 and 5% albumin, approximately between 1 and 2% dextrose, and further comprising the perfluorocarbon gas, decafluorobutane or oxygen and a nucleic acid for delivery. Microbubbles comprising albumin are not representative or correlative of the broad genus comprising any filmogenic protein encapsulated microbubbles. The disclosure does not clarify the common attributes encompassed by the genus comprising filmogenic protein encapsulated microbubbles. The specification does not describe the elements essential to this broad genus, nor does it indicate the distinguishing attributes concisely shared by members of this broad genus. Thus, the scope of the claims includes numerous structural variants, the genus is highly variant because a significant number of structural differences between members of the genus is permitted. Concise structural features that could distinguish structures within the genus from those outside of it are missing from the disclosure. No common structural attributes identify the members of the genus comprising a plurality of filmogenic protein encapsulated insoluble gas filled microbubbles. The specification fails to teach or adequately describe a representative number of species in the genus such that the common attributes or characteristics concisely identifying members of the

proposed genus are exemplified. And because the genus is highly variant, the description provided is insufficient. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus claimed. Thus Applicant was not in possession of the claimed genus.

Claims 37-42 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of delivering a nucleic acid to the liver of a mammal comprising the intravenous administration of a microbubble comprising approximately between 3 and 5% albumin, approximately between 1 and 2% dextrose, and further comprising the perfluorocarbon gas, decafluorobutane or oxygen and a nucleic acid for delivery, and being enabled for a method for delivering an oligonucleotide targeting c-myc to a site of endothelial injury or thrombosis comprising intravenous administration of a composition comprising microbubbles comprising approximately between 3 and 5% albumin, approximately between 1 and 2% dextrose, and further comprising the perfluorocarbon gas, decafluorobutane or oxygen and an antisense oligonucleotide that specifically targets a nucleic acid encoding c-myc, does not reasonably provide enablement for methods for delivery, to any tumor site in an organism, a composition comprising any biological agent or medicament conjugated to any filmogenic protein, and which composition further comprises a plurality of filmogenic protein-encapsulated insoluble gas filled microbubbles, wherein the biological agent or medicament is encapsulated within the microbubbles and delivered to any tumor site in an organism.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claims are drawn to methods for delivery, via any route of administration, to any tumor site in an organism, any composition comprising a plurality of filmogenic protein-encapsulated insoluble, perfluorocarbon or SF_6 gas filled microbubbles, wherein a medicament or biological agent is optionally bound to the filmogenic protein.

The following factors have been considered in determining that the specification does not enable the skilled artisan to make and/or use the invention over the scope claimed. This determination is based on several factors which, when considered together, illustrate that the art of biological agent delivery using any filmogenic protein encapsulated microbubbles is highly unpredictable.

The state of the prior art and the predictability or unpredictability of the art. General disadvantages of biological agent delivery *in vivo* include a lack of sufficient data regarding cell targeting, cell entry and gene expression in appropriate target cells as well as poor efficiency of delivery and the transient expression of delivered genes. These disadvantages pertain also to the use of protein encapsulated microbubbles for biological agent delivery. The following references are cited herein to illustrate the state of the art of treatment in organisms that involves the delivery of effector molecules to appropriate cells in an organism. Branch and Crooke teach that the in vivo (whole organism) application of nucleic acids (such as antisense) is a highly unpredictable endeavor due to target accessibility and delivery issues. Crooke also points out that cell

culture examples are generally not predictive of in vivo inhibition of target genes. (A. Branch, Trends in Biochem. Sci. 23: 45-50, document "BA" in IDS filed 11-17-03, *see* entire text for Branch; S. Crooke, Antisense Res. and Application, Chapter 1, pp. 1-50, especially at 34-36).

Likewise, Peracchi cautions investigators in the field of gene therapy about the problems of achieving in vivo efficacy using oligonucleotide based approaches Peracchi cites stability and delivery obstacles that need to be overcome in achieving desired in vivo efficacy: "A crucial limit of ribozymes in particular, and of oligonucleotide-based drugs in general, lies in their intrinsically low ability to cross biological membranes, and therefore to enter the cells where they are supposed to operate...cellular uptake following systemic administration appears to require more sophisticated formulations... the establishment of delivery systems that mediate efficient cellular uptake and sustained release of the ribozyme remains one of the major hurdles in the field." (A. Peracchi et al, Rev. Med. Virol., 14: 47-64, especially at 51).

Agrawal et al also speak to the unpredictable nature of the nucleic acid based therapy field thus: AIt is therefore appropriate to study each ... oligonucleotide in its own context, and relevant cell line, without generalizing the results for every oligonucleotide (S. Agrawal et al., Molecular Med. Today, 6: 72-81 at 80). Cellular uptake of oligonucleotides by appropriate target cells is another rate limiting step that has yet to be overcome in achieving predictable clinical efficacy using antisense." Both Chirila et al and Agrawal et al point to the current limitations which exist in our understanding of the cellular uptake of ... oligonucleotides in vitro and in vivo (see Agrawal et al

especially at pages 79-80; *see* Chirila et al., Biomaterials, 23: 321-342 in its entirety, especially at 326-327 for a general review of the important and inordinately difficult challenges of the delivery of therapeutic oligonucleotides to target cells).

The amount of direction or guidance presented in the specification and the presence or absence of working examples. Applicants have not provided guidance in the specification toward a method of delivering the broad genus of compositions claimed, nor a representative number of species thereof, to any tumor site in an organism comprising the administration of microbubbles comprising any filmogenic protein encapsulating insoluble gas microbubbles and further comprising any medicament or biological agent optionally bound to the filmogenic protein and encapsulated within the microbubbles.

The specification teaches the successful targeting to liver of antisense comprising the intravenous administration to a mammal of antisense in a microbubble comprising a plurality of albumin (approximately 3-5%) in combination with dextrose (approximately 1-3%), whereby perfluorocarbon gas decafluorobutane or oxygen is encapsulated by the albumin, and further whereby the antisense is delivered to the liver, expression of the target gene is inhibited and biological effects are provided. The disclosure also teaches the delivery of albumin-encapsulated, perfluorocarbon or SF_6 gas filled microbubbles comprising anti-c-myc antisense to a site of endothelial injury or thrombosis comprising the intravenous administration of this particularly described albumin-encapsulated microbubble composition. The specification fails to teach the successful delivery of a biological agent to any tumor site in an organism comprising the

administration of the broadly claimed genus of compositions comprising microbubbles comprising any filmogenic protein encapsulating insoluble gas, and further comprising any medicament or biological agent optionally bound to the filmogenic protein and encapsulated within the microbubbles.

One skilled in the art would not accept on its face the examples given in the specification of the successful targeting to liver of antisense comprising the administration to a mammal of antisense in a microbubble comprising a plurality of albumin (approximately 3-5%) in combination with dextrose (approximately 1-3%), whereby the perfluorocarbon gas decafluorobutane is encapsulated by the albumin, or the delivery of such microbubbles comprising c-myc antisense to sites of thrombosis or endothelial injury comprising intravenous administration of these microbubble compositions as being correlative or representative of the administration by any route of any medicament or biological agent encapsulated within a microbubble comprising any filmogenic protein, such that the biological agent is appropriately and specifically delivered to any tumor in an organism. This is in view of the lack of guidance in the specification and known unpredictability associated with the administration by any route to any organism of a microbubble comprising a plurality of any filmogenic protein encapsulating any biological agent and an insoluble gas. The specification as filed fails to provide any particular guidance which resolves the known unpredictability in the art associated with *in vivo* delivery of any biological agent to a specific target tumor comprising the administration of a representative number of species of the large genus of compositions claimed comprising microbubbles comprising any filmogenic protein,

and further whereby any biological agent or medicament is delivered to any tumor site in an organism.

The breadth of the claims and the quantity of experimentation required. The claims are drawn to methods of delivery, to any tumor site in an organism, of a composition comprising any biological agent or medicament optionally bound to any filmogenic protein, and which biological agent or medicament is encapsulated within the microbubbles..

In order to practice the invention over the scope claimed, it would require trial and error or undue experimentation beyond which is taught in the specification to practice the invention drawn to the delivery to any tumor site in an organism, via any route of administration, a composition comprising a plurality of filmogenic protein-encapsulated insoluble, gas filled microbubbles, wherein any biological agent or medicament is optionally bound to any filmogenic protein. The quantity of experimentation required to practice the invention as claimed would require the *de novo* determination of accessible target sites, modes of delivery, whereby a representative number of species of the large genus of microbubble compositions claimed are successfully delivered to any tumor site via any route of administration. Since the specification fails to provide any particular guidance for the successful delivery to any tumor site of a representative number of species of the broad genus of compositions claimed, by any route of administration, and since determination of these factors for the successful delivery to a tumor site of a particular filmogenic protein encapsulating a

medicament or biological agent is highly unpredictable, it would require undue experimentation to practice the invention over the scope claimed.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 43-46 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-10 of U.S. Patent No. 6,117,858. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims and those of U.S. Patent No. 6,117,858 are both drawn to compositions comprising filmogenic protein encapsulated, gas insoluble microbubbles for the delivery of medicaments or biological agents, which agents are optionally bound to the filmogenic protein, and which are encapsulated within the microbubbles.

Claims 43-46 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 8-13 of U.S. Patent No.

5,849,727. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims and those of U.S. Patent No. 5,849,727 are both drawn to compositions comprising filmogenic protein encapsulated, gas insoluble microbubbles for the delivery of medicaments or biological agents, which agents are encapsulated within the microbubbles.

Claims 43-46 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 12-17 of U.S. Patent No. 6,537,814. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims and those of U.S. Patent No. 6,537,814 are both drawn to compositions comprising filmogenic protein encapsulated, gas insoluble microbubbles for the delivery of medicaments or biological agents, which agents are optionally bound to the filmogenic protein and which are encapsulated within the microbubbles.

Claims 43-46 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 2, 4-6 and 8 of copending Application No. 10/355,388. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims are drawn to compositions comprising protein encapsulated, gas insoluble microbubbles for the delivery of oligonucleotides, which oligonucleotides are conjugated to the protein at the microbubble surface, and claims 1, 2, 4-6 and 8 of copending Application No. 10/355,388 are drawn to compositions comprising oligonucleotides conjugated to the

surface of a filmogenic protein which is encapsulated within a gas insoluble microbubble.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.Claims 37-42 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-7 and 14 of U.S. Patent No. 5,894,727. Although the conflicting claims are not identical, they are not patentably distinct from each other insofar as the instant claims and the claims of U.S. Patent No. 5,894,727 are both drawn to methods for delivery of a biological agent to a site in an organism comprising administration of biological agents optionally bound to filmogenic protein encapsulated, gas insoluble microbubbles.

Claims 37-42 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-11 and 18-23 of U.S. Patent No. 6,537,814. Although the conflicting claims are not identical, they are not patentably distinct from each other insofar as the instant claims and the claims of U.S. Patent No. 6,537,814 are both drawn to methods for delivery of a biological agent to a site in an organism comprising administration of biological agents optionally bound to filmogenic protein encapsulated, gas insoluble microbubbles.

Conclusion

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94

(December 28, 1993) (see 37 C.F.R. 1.6(d)). The official fax telephone number for the Group is **571-273-8300**. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jane Zara** whose telephone number is **(571) 272-0765.** If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras, can be reached on (571) 272-4517. Any inquiry regarding this application should be directed to the patent analyst, Katrina Turner, whose telephone number is (571) 272-0564. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jane Zara
6-8-06